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## Review Article

## Antiviral performance of graphene-based materials with emphasis on COVID-19: A review



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## ABSTRACT

Coronavirus disease-2019 has been one of the most challenging global epidemics of modern times with a large number of casualties combined with economic hardships across the world. Considering that there is still no definitive cure for the recent viral crisis, this article provides a review of nanomaterials with antiviral activity, with an emphasis on graphene and its derivatives, including graphene oxide, reduced graphene oxide and graphene quantum dots. The possible interactions between surfaces of such nanostructured materials with coronaviruses are discussed. The antiviral mechanisms of graphene materials can be related to events such as the inactivation of virus and/or the host cell receptor, electrostatic trapping and physico-chemical destruction of viral species. These effects can be enhanced by functionalization and/or decoration of carbons with species that enhances graphene-virus interactions. The low-cost and large-scale preparation of graphene materials with enhanced antiviral performances is an interesting research direction to be explored.

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## 1. Coronaviruses; structure, transmission and taxonomy

During the last two decades, coronaviruses (CoVs) have been the cause of local and global epidemics, including Severe Acute Respiratory Syndrome (SARS) [1–6], Middle East Respiratory Syndrome (MERS) [7–10], and Porcine epidemic diarrhea virus (PEDV) with the mortality rate around 10%, 35% and 95% respectively, threatening human health and economic well-being. For instance, the latter caused

ten percent reduction of pig population in the USA in 2013 [11,12]. Currently, the pandemic outbreak of the febrile respiratory disease, so called COVID-19 [13,14] has created a global transmission network, leading to an international crisis related to the catastrophic losses of human lives and financial meltdowns. As such, the exploration of effective antiviral agents that can be effective on COVID-19 is of great importance. Given this, the current article concerns the potential capability of graphene-based materials for antiviral therapy applications.

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To this end, first a brief review on the basic aspects associated with coronaviruses is made, based on which the influences of drugs are discussed.

Coronaviruses are categorized as pleomorphic enveloped viruses with single-strand positive sense RNA genome ranging 26–32 kb in size [15–18]. The genome of CoVs is packaged into a helical capsid surrounded by a virion envelope, containing at least three proteins including the spike, membrane and envelope-types proteins. The schematic representation of coronavirus virion structure, and spike proteins are illustrated in Fig. 1 [19,20].

Furthermore, other types of proteins such as hemagglutinin esterase may also exist on CoVs. It should be mentioned that the membrane and envelop proteins are considered as transmembrane proteins that are important in the virus assembly. In contrast, the spike proteins play an essential role to infect the host cells [19–21]. The structure of spike proteins available on the surface of virion is shown in Fig. 1b, in which the crown shaped protein is formed of two domains, namely an amino (N)-terminal domain (subunit S1), and a carboxy (C)-terminal domain (subunit S2). Subunit S1 is responsible for binding of the virus to the host cell receptors, while subunit S2 causes the membrane fusion that allows entering viral genomes into the host cell [19,22,23]. Therefore, COVID-19 can infect human cells through binding of its S proteins to human ACE2 (angiotensin converting enzyme 2) receptor, which is a transmembrane protein on the cell surface [24,25].

The explosive nature of COVID-19 transmission can be correlated to its biological features. In this regard, CoVs is of the order *Nidovirales*, *Coronaviridae* family, and the *Coronavirinae* subfamily. The latter can be classified into four genera of alphacoronavirus, betacoronavirus, deltacoronavirus, and gammacoronavirus [20,21,26–29]. The first two are the pathogenic agents for mammals, the third one would affect the avian and mammalian species, and the last one infects birds [20,30]. The gene source for alpha- and betacoronavirus are bats whereas birds are the gene source for gamma- and deltacoronavirus [30,31]. Ye et al. [32] reported that wild birds like sparrows can also be involved in transmission of porcine deltacoronavirus to pigs [32], highlighting the complexity of the transmission chain. Likewise, civets and camels have been reported to be able to serve as the intermediate hosts for SARS-CoVs and MERS-CoVs, respectively, further highlighting the potential for interspecies transmission [33–35]. Similarly, bats and snakes may act as intermediate hosts for case of COVID-19 [36,37].

## 2. Animal and human infectious coronaviruses

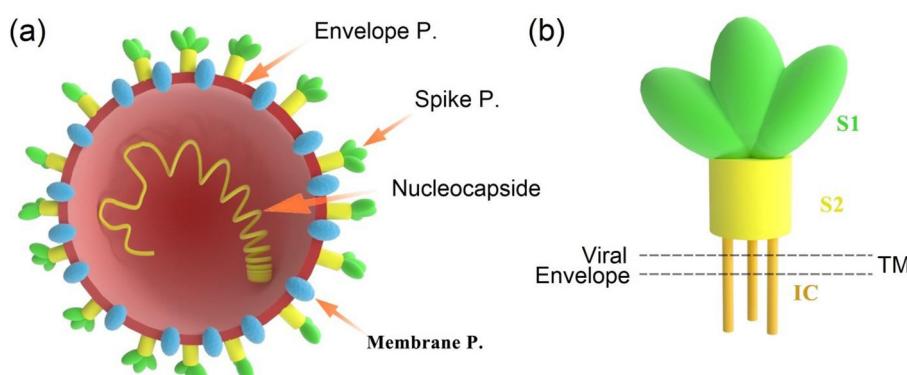
Coronaviruses can be the source of infection in animal and human populations. Here we briefly review these viruses. In terms of animal

infectious coronaviruses, alphacoronaviruses include transmissible gastroenteritis virus [38], porcine-respiratory coronavirus [39] and porcine-epidemic diarrhea virus [40] infecting pigs; feline-CoV affecting cats [41]; bat coronaviruses such as *Scotophilus* bat CoV-512, *Rhinolophus* bat CoV-HKU2, *Miniopterus* bat CoV 1A/B and CoV-HKU8 infecting various species of bats [42–45].

For the case of betacoronaviruses, there are four subgroups of A, B, C and D. The subgroup A includes bovine-coronavirus (BCoV) in cows [46], porcine hemagglutinating encephalomyelitis virus in pigs [47], equine CoV in horses [48,49], mouse hepatitis CoV in rodents [50] and rabbit CoV-HKU14 in domestic rabbits [51]. Moreover, SARS-related *Rhinolophus* bat CoV-HKU3 belongs to the subgroup B [52], while *Tylonycteris* bat CoV-HKU4 and *Pipistrellus* bat CoV-HKU5 belong to the subgroup C [53–55]. The subgroup D of betacoronaviruses include *Rousettus* bat CoV-HKU9 [55,56]. On the other hand, infectious bronchitis virus, turkey coronavirus, beluga whale coronavirus SW1 and bottlenose dolphin CoV-HKU22 are members of genus gammacoronavirus [57–60]. Also, avian infectious deltacoronaviruses include bulbul CoV-HKU11, thrush CoV-HKU12, munia CoV-HKU13, white-eye CoV-HKU16, sparrow CoV-HKU17, magpie robin CoV-HKU18, night heron CoV-HKU19, wigeon CoV-HKU20 and common moorhen CoV-HKU21 [30,61]. In addition, porcine deltacoronavirus infects pigs [62,63].

Human coronaviruses (HCoVs) can cause severe infections, as for the case for COVID-19. HCoVs include HCoV-229E, HCoV-NL63 (alphacoronavirus), HCoV-OC43, HCoV-HKU1 (betacoronavirus-A), HCoV-SARS (betacoronavirus-B), as well as HCoV-MERS (betacoronavirus-C) [30,33,34,53,54,64,65]. It should also be mentioned that various bat species are reported to be the origin of different human coronaviruses [66,67]. Recently, the International Committee on Taxonomy of Viruses (ICTV) has divided the genus betacoronavirus into five subgenera, namely embecovirus, sarbecovirus, merbecovirus, nobecovirus and hibecovirus. Based on this, SARS-CoV and COVID-19 belong to the subgenera sarbecovirus and MERS is the member of subgenus merbecovirus [68,69].

It should be mentioned that coronaviruses generally cause respiratory, gastrointestinal, hepatic, and central nervous system diseases in humans and animals with various severity [13,57,63,70]. The clinical symptoms of HCoV often include one or more of fever, cough, sneeze, respiratory distress, wheeze, pharyngitis, nasal discharge, nasal congestion, sputum, rhinorrhea, chills, muscle aches, headache, and gastrointestinal tract symptoms [71–84]. COVID-19 can cause additional issues such as loss of taste/smell, nausea and vomiting, anorexia, liver dysfunction, hyperglycaemia, septic shock and ventilator-associated pneumonia [85–90] as well as conjunctivitis [91,92]. The emergence of new versions of coronaviruses, threatening



**Fig. 1.** The schematic illustration of (a) the typical coronavirus virion structure, highlighting the presence of three types of proteins marked as "P." generated based on information extracted from [19]. (b) Coronavirus spike protein; subunit S1: the receptor-binding, subunit S2: the membrane-fusion; TM: the transmembrane anchor; IC: the intracellular tail and the viral envelope generated based on information extracted from [20].

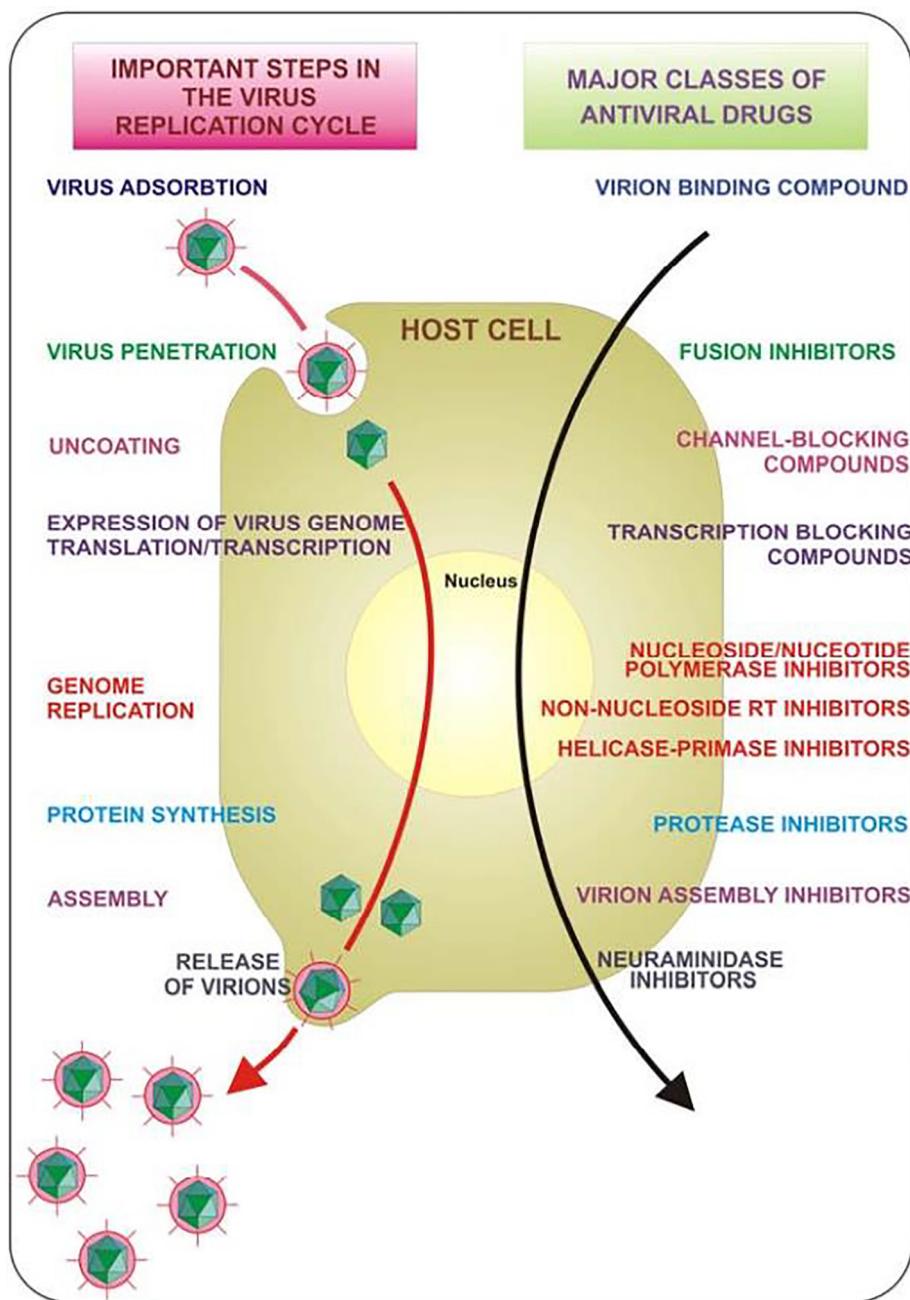
the human and animal health, has highlighted the importance of the discovery of effective antiviral agents, as will be discussed in the next section.

### 3. Antiviral strategies against coronaviruses

The effective fight against viruses requires the detailed knowledge of ways through which the virus can invade host cells. This involves three main steps of (a) the cellular attachment and entry, (b) the replication of viral genome and viral proteins expression, and (c) the assembly, maturation, and exocytosis. Therefore, viruses rely on their

host cell proteins and processes based on the above mentioned mechanisms [93]. Fig. 2 illustrates the essential steps involved in the virus replication cycle [94]. This can also highlight possible ways to combat against viruses, based on which, an effective antiviral material should inhibit at least one of the virus replication cycles.

As presented in the right side of Fig. 2, an antiviral target may attack a virus at any stage of its replication cycle. Not to mention that targeting the early steps of the virus entry is considered as an appropriate strategy for therapeutic intervention. It is because the inhibitor can attack the virus extracellularly, providing a larger accessibility to the virus, and less damage to the host cell [94].



**Fig. 2.** The schematic illustration of possible steps involved in the virus replication cycle as well as possible ways by which viruses can be inactivated. Accordingly, the virus first binds to the cell. Subsequently, the virus or its genome enters in the cytoplasm of the cell, followed by the liberation of the genome from its protective capsid. It is then transcribed, and the viral mRNA directs the host cell to synthesize viral enzymes and capsid proteins, and to assemble new virions, which are then released from the cell. The virus can be targeted by antiviral drugs at each step of the cycle mentioned above, as shown in the right side of the image [94].

For the case of COVID-19, like any other new infectious disease without definitive and/or effective treatments, two major strategies are considered to counteract the infection, based on drug repurposing and the discovery of novel drugs. Drug repurposing can be a feasible strategy for combating epidemic diseases, since it considerably shortens the time of drug development, supporting a swift response to the spread of the novel virus species. As an example of the drug repurposing for COVID-19, one can indicate metal-based drugs which have been suggested as promising candidates to control the coronavirus [95]. Metallodrugs such as the gold drug auranofin (2,3,4,6-tetra-o-a-cetyl-L-thio-β-D-glycol-pyranoses-S-(triethyl-phosphine)-gold(I)) has shown antiviral influences against COVID-19 *in vitro* [96]. However, the general problems associated with the use of metal compounds is valid here as well, including the systemic toxicity [97]. Based on molecular mechanics-assisted structure-based virtual screening method, Terali et al. [98] reported a list of drug repurposing candidates which can be used as inhibitors of COVID-19. These drugs include lidofovir, quinostat, spirofylline, burixafor, pemetrexed, edotecarin, dinoprofylline and fluprofylline [98].

Furthermore, some medicines such as chloroquine, hydroxychloroquine, remdesivir, tocilizumab and lopinavir/ritonavir have shown controlling effects on COVID-19 patients [99–104]. In addition to these, zinc supplements exhibit inhibitory effects on the replication of COVID-19 in infected cells, when used with chloroquine [105]. While this strategy of treating COVID-19 is promising, further examinations should be conducted in order to evaluate the performances and side effects of such drugs which may appear in the presence of the new virus species.

Computational simulations can provide valuable information that is difficult or expensive to be obtained experimentally. Speciale et al. [106] conducted a fundamental study based on the computational analysis, and reported on the potential of silibinin to prevent COVID-19 entry into cells due to the formation of a stable complex between COVID-19 spike protein receptor binding domain (RBD) and silibinin. Moreover, silibinin was found to be effective for inhibiting COVID-19 replication due to interactions with aminoacidic residues on the active site of COVID-19 main protease [106]. Another study based on the molecular docking showed that doxepin could inhibit viral entry into the host cells due to binding to ACE2. In this case, doxepin exhibits hydrophobic interactions, and supports hydrogen bonding with COVID-19 spike protein RBD [107]. Another molecular simulation-based research demonstrated the inhibitory ability of glucocorticoids (betamethasone, dexamethasone, hydrocortisone, fludrocortisone, ciclesonide and triamcinolone) against COVID-19 via binding interactions between the selected glucocorticoids and COVID-19 main protease pocket amino acids [108]. A combination of such computational analyses using the available drugs with sufficient experimental trials is required for the successful delivery of efficient drugs for new viruses.

The second strategy in combating COVID-19, which is based on discovering novel drugs, is more complicated and time consuming. It is because the process of new drug discovery requires more fundamental theoretical studies, the production of new drugs and various evaluations to confirm the efficiency of the developed drugs *in vitro*, then *in vivo*. Furthermore, additional experiments are needed to ensure the biocompatibility as well as environmental safety of such drugs, leading to the requirement for additional funding and time. Despite these limitations, the second strategy of combating new viral infections has the higher potential of providing drugs with unique advantageous properties, than those currently available. In this regard, strengthening the immune system can be an important factor in reducing the mortality of viral diseases, which may be combined with herbal drugs. The latter can be produced from various parts of plants such as seeds, barks, flowers, roots, stems, and fruits for immunomodulating and strengthening the immune system [109,110]. Moreover, the alkaloids, flavonoids and polyphenol exist in some plants such as garlic,

peppermint, oregano, ginger, licorice, tulsi, turmeric, echinacea, astragalus, and fennel can cause the release of antibodies and interferons toward viral infections [109]. For instance, Echinaforce®, a herbal medicine derived from *Echinacea purpurea*, has been shown to be effective in inactivation of HCoV-229E, MERS-CoV, SARS and COVID-19 at least *in vitro* [111]. Also, based on the molecular docking technique, Thuy et al. [112] reported the inhibitory effect of garlic essential oil toward COVID-19 due to the strong interactions between the 17 organosulfur compounds of the garlic essential oil and the amino acids of the ACE2 protein as well as the main protease PDB6LU7 of COVID-19.

Furthermore, organometallic compounds such as sodium copper chlorophyllin synthesized from chlorophyll show antibacterial and antiviral activity [113,114]. An enhanced level of antiviral activities can be achieved using nanomaterials, as discussed in the next section.

#### 4. Application of nanotechnology in virus therapy

Nanotechnology has been playing a vital role in the recent progress of biomedicine and bioengineering, including the synthesis and application of therapeutic nanomaterials for various applications such as cancer diagnosis and therapy, drug delivery and tissue engineering [115–117].

Likewise, nanotechnology and nanoscience may open new windows in combating various pathogens including COVID-19, in different ways such as detecting the virus, diagnosis of viral infection and nano-vaccines, such as lipid nanoparticles, for the prevention and/or the therapy of COVID-19 infection [118–129].

In general, two approaches can be distinguished in the application of nanomaterials against viruses. One approach considers an external stimulus which can kill viruses [130]. The other approach is related to the interaction between the surfaces of the viruses and the nanomaterial employed as the antiviral agent.

The first approach may be implemented by the application of light or Near Infrared (NIR) irradiation. For example, Akhavan et al. [131] reported on the photoinactivation performance of thin films of graphene–tungsten oxide nanocomposites against bacteriophage MS2 viruses under visible light irradiation. In this case, the protein capsid photodegradation and effluxion of the RNA are identified as the mechanisms of bacteriophage MS2 virus inactivation [131].

The second approach highlights the antiviral performances of nanostructured materials. It was reported that human coronaviruses can survive on non-living surfaces, including glass-, plastic- or metal-surfaces for nine days [132]. Therefore, using surfaces with the ability to kill pathogens would be highly beneficial to prevent the spread of infections. Perhaps one of the first reports on the impact of nanostructured topography toward COVID-19 was presented by Hasan et al. [133] who demonstrated the antiviral performance of the surfaces of nanostructured aluminium 6063 alloy against COVID-19. The alloy was synthesized by the wet etching technique. The use of such nanostructure surfaces can be an interesting approach toward the reduction of environmental contaminations and hospital infections, and consequently, the transmission of COVID-19. Copper alloy surfaces are also reported to possess anti-pathogenic performance, reducing the infectious disease transmission from fomites [132,134–137]. The surfaces of copper alloy, therefore, may limit the spread of COVID-19 [138]. As for comparison, COVID-19 could survive for three days on plastic and stainless steel surfaces, but no live COVID-19 could be detected on copper alloy surfaces only after four hours of exposure [139]. In fact, copper has been shown to have antiviral ability against both enveloped and nonenveloped various genomes (single or double strand DNA and RNA) such as human immunodeficiency virus type 1 (HIV-1), bronchitis virus and poliovirus [140,141].

As another example of metallic materials with antiviral performance, one can name silver nanoparticles. Immunofluorescence studies confirmed that the polyvinylpyrrolidone polymer coated with

10 nm silver nanoparticles could inhibit COVID-19 infection towards VeroE6/TMPRSS2 cells. Here, the effect of nanostructuring was highlighted, since the application of silver particles with sizes around 100 nm could not provide an appropriate antiviral performance [142].

Apart from alloys and coatings, the antiviral performances of nanoparticles in powder forms have also been of interest. For instance, silver nanoparticles with the sizes of 2–15 nm exhibit antiviral activity against COVID-19 [142]. However, since metallic nanoparticles are highly reactive in powder forms, the application of metal oxide powders is of importance. As a good example in this field, one can indicate the antiviral performance of tin oxide ( $\text{SnO}_2$ ) nanowires against HSV-1 infection. In this case,  $\text{SnO}_2$  nanowires work as a carrier of negatively charged structures that compete with HSV-1 attachment to cell bound heparan sulfate, and therefore, inhibit the entry and the subsequent cell-to-cell spread [143].  $\text{SnO}_2$  has also been used for the destruction of antiviral drugs, such as abacavir after the treatment of HIV [144]. The strategy of using metal oxide nanostructures is attractive, since such materials can be produced at low-cost using environmentally friendly approaches [145–147]. As another example of using metal oxides, Abo-zeid et al. [148] reported on the potential application of iron oxide nanoparticles to inactivate COVID-19. Their results obtained using molecular docking studies show that both  $\text{Fe}_2\text{O}_3$  and  $\text{Fe}_3\text{O}_4$  are able to interact with the spike protein of COVID-19 (subunit S1 in Fig. 1b), but  $\text{Fe}_3\text{O}_4$  binding was found to be more stable. According to this study, under the influence of iron oxide nanoparticles, COVID-19 can lose its ability to attach to the host cell receptors [148].

It follows from what is mentioned above that the characteristics of surfaces of nanostructured materials can provide a critical influence on their antiviral performances. In fact, the application of non-toxic substances that can effectively combat COVID-19 and future viral outbreaks should be very important towards the control of virus infections. One of those non-toxic nanomaterials is graphene, as discussed in next sections.

## 5. Graphene-based materials

As an interesting member of carbon nanostructures, graphene, the building block of graphite, can be defined as an atomically two-dimensional layer of hexagonally bonded carbon atoms. Such carbon structure can exhibit outstanding properties such as large specific surface area, high mechanical strength, high electron conductivity as well as strong thermal, optical and catalytic characteristics [149–160]. Graphene-based materials are referred to those materials that contain single or few-layer graphene or graphene oxide [161,162] in their structures. Furthermore, high quality graphene materials may be produced at large scales using low cost methods that employ highly available resources such as graphite [163,164], biomass [165] and waste plastics [166,167], making them attractive for commercial applications.

These unique properties of graphene and its derivatives have made these nanostructured materials suitable for various biological and medical applications [168] including anti-pathogenic applications [169–177], biosensors [178–184], bioimaging [185–192], tissue engineering [193–196], drug delivery [197–201]. Therefore, the interactions between graphene materials and viruses should be of great interest.

It should be mentioned that the antibacterial activity of graphene nanomaterials can be explained based on various effects including membrane-, oxidative-, and/or photothermal- stresses as well as charge transfer, and the entrapment effect of graphene materials on various bacterial species, as recently reviewed elsewhere [255]. In comparison with bacteria, relatively very little is known about the antiviral performances of graphene materials, mainly because of significant differences in the size of virus (2–300 nm) and bacteria (500–5000 nm), which makes the viral studies more difficult and/or expensive to be conducted [256,257]. This article reviews the antiviral activity of graphene nanomaterials, based on the available literature.

## 6. Interactions between graphene-based materials and viruses

As briefly discussed above, graphene-based materials can be used in various biomedical fields, including the rapid and accurate detection of virus species, personal protective equipment such as masks, gowns and gloves, as well as the antiviral applications [202–210]. One important and common aspect of these studies is related to the interactions between the virus and graphene-based materials.

Chowdhury et al. [211] reported on the electrochemical detection of Hepatitis E virus (HEV) by a graphene-based nanocomposite, defined as nitrogen- and sulfur-co-doped graphene quantum dots (QDs) and gold embedded polyaniline nanowire [211]. Here, gold nanoparticles loaded polyaniline nanowire enhances the electron transfer process and provides a large surface area on which the monoclonal antibody-conjugated graphene QDs can be loaded. The latter could provide active sites for the target HEV. Introducing an external electrical pulse during the virus accumulation step increases the sensitivity of the antiviral agent towards HEV compared to other conventional electrochemical sensors. It is because the external electrical pulse can cause the expansion of the surface of the virus as well as the length of the antibody-conjugated polyaniline chain [211]. This research may highlight the capability of graphene QDs (with sizes of around 500 nm) to be effectively attached to the virus species.

This example highlights that interactivity of graphene with surrounding environment plays a key role in the overall performance of the material. It should be mentioned that graphene edge can be of particular interest due to the presence of dangling bonds, representing at least two times greater reactivity in comparison with the basal plane [212,213].

In contrast with graphene, graphene oxide (GO) is the oxidized form of graphene with hydroxyls, epoxides, diols, ketones, or carboxyls functional groups located on its surface. The presence of oxygen on the edges and basal planes of GO increases its hydrophilicity, water dispersibility, and attachability in comparison with graphene [214,215]. Given this, Song et al. [216] further highlighted the capability of GO to capture EV71 (the agent of hand, foot and mouth disease) and  $\text{H}_9\text{N}_2$  (the agent of avian influenza A virus) at 56 °C. GO was found efficient for the destruction of the coating proteins available on these viruses and extracting the viral RNA in an aqueous environment. This interaction leads to the superficial bioreduction of GO, leading to its conversion into graphene form, while killing the virus [216].

It should be mentioned that the graphene formed by the reduction of GO is often called reduced graphene oxide (rGO). The reduction of GO can also occur during thermal reduction treatments [217,218].

Ziem et al. [219,220] produced thermally rGO sheets functionalized by polysulfated dendritic polyglycerol. This functionalized rGO material showed antiviral performance against a range of viruses comprising orthopoxviruses, herpes simplex virus type 1 (HSV-1) and equine herpesvirus type 1 (EHV-1). These viruses cause the significant global health problems such as HSV-1 and orthopoxviruses that infect humans, and EHV-1 that infects horses. It was demonstrated that the binding of polar polymers to the carbon material leads to enhanced solubility in water. It also results in a bioinert multifunctional surface that is easily accessible for further post-modification and biological interactions. The subsequent sulfation of the material promotes the interaction of the material with viruses. Here, graphene scaffolds with the large surface area provide the opportunity to increase the valency of the dendritic polyglycerol sulfate groups [219,220].

As shown in Fig. 1, for the binding and entering of viruses into the host cell, the virus must first interact with the host cell surface receptors. In viral envelope glycoproteins, heparan sulfate proteoglycans and chondroitin sulfate proteoglycans function as the cell surface receptors [221,222]. Given this, functionalized graphene materials can prevent cellular viral infections based on the interaction between

negatively charged functional groups which mimic cell surface heparan sulphate [219,220]. In addition to this, the size of graphene flakes and the degree of sulfation could influence the antiviral activity of the functionalized graphene materials. Accordingly, the flake sizes of around 300 nm together with around 10% functionalization could provide the optimum performance [220].

Elechiguerra et al. [223] coated silver nanoparticles with carbon, bovine serum albumin and poly N-vinyl-2-pyrrolidone, and evaluated the antiviral performances of the resultant materials against HIV-1 virus. Out of these samples, carbon coated silver nanoparticles showed a higher level of antiviral performance [223], which could be related to their surface chemistry, providing a higher reactivity against the virus.

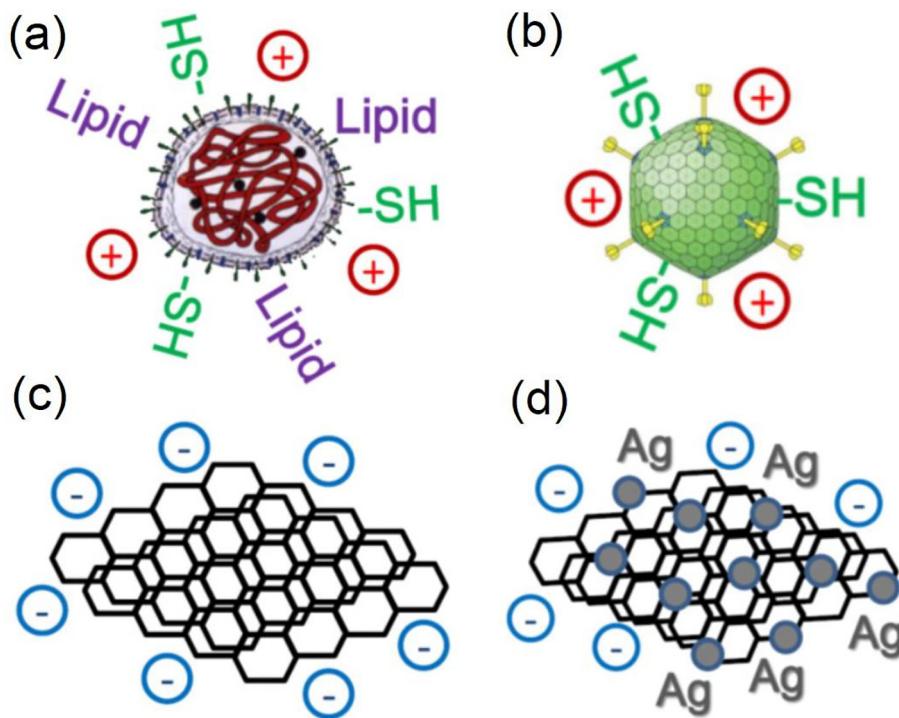
The feline coronavirus (FCoV), and the infectious bursal disease virus (IBDV) have been used to evaluate the antiviral performances of graphene materials. FCoV belongs to the genus alphacoronavirus with its positive-sense, single-stranded RNA and a lipid envelope (Fig. 3a). Cats show feline infectious peritonitis because of this virus, and the spread of the virus is possible through the direct contact with infected secretions [224]. IBDV is a member of the family *Birnaviridae* and the genus *Avibirnavirus*. It is a non-enveloped virus with double-stranded RNA (Fig. 3b) [225,226]. This virus is responsible for the infectious bursal disease, also called Gumboro disease in young chickens, inducing immunosuppression, leading to a significant economic losses [227,228].

Chen et al. [229] evaluated the antiviral activity of GO and GO-Ag nanocomposites against FCoV and IBDV. The schematic structures of these viruses as well as the graphene-based antiviral species are shown in Fig. 3. It was found that GO-Ag exhibits a higher level of antiviral activity than GO. Accordingly, the GO-Ag nanocomposite was capable of controlling FCoV and IBDV by 25% and 23%, respectively; whereas GO only showed 16% inhibition of FCoV and no inhibition against IBDV. Antiviral mechanism involved in the antiviral performance of GO and GO-Ag could be explained based on the structural features, highlighted in Fig. 3. The antiviral performances of graphene materials

could be explained based on chemical/physical interactions with viruses. Based on this, the opposite surface charges of antiviral species (GO and GO-Ag) from one side, and both viruses from the other side, could cause binding between graphene materials and viruses. Under this condition, GO could interact with the lipid molecules of the enveloped virus. Additionally, the binding of Ag and -SH groups of viral proteins in both enveloped and non-enveloped viruses provides an additional interaction. This binding is critical in order to control the infection of IBDV. For the case of GO-Ag and non-enveloped viruses, GO nanosheets play a minimal direct role in the overall antiviral activity of the nanocomposite. Instead, GO contributes to the overall performance of the antiviral agent by providing a substrate for silver particles to be well dispersed without obvious aggregation [229]. Further investigations confirm the electrostatic interactions between GO/rGO species and oppositely charged lipid membranes, leading to the adsorption of graphene materials followed by the rupture of the liposome [230,231].

Such an electrostatic force-driven interaction has also been described for the case of porcine epidemic diarrhea virus with positive-strand RNA genome from genus alphacoronavirus, and also the pseudorabies virus with double stranded DNA genome from genus alphaherpesvirus [232]. Here, the antiviral mechanism of GO against these viruses was discussed to be based on the interaction between negatively charged surfaces of GO with sharp edges, and positively charged viruses. It should also be noted that GO could only show an antiviral activity if used before the viral absorption, so that the application of GO simultaneously or after viral infection, had no effect on the infection [232].

As another example, Sametband et al. [233] reported that the charge density is the most important factor influencing the antiviral properties of GO and rGO-SO<sub>3</sub> against HSV-1. Both graphene materials mentioned above could prevent the attachment of the viruses to host cell surface receptors, mimicking heparan sulfate biological activities. It should be added that the heparan sulfate, GO and rGO-SO<sub>3</sub> all have a negative charge [233].



**Fig. 3.** The schematic illustration of (a) the enveloped feline coronavirus, (b) the non-enveloped infectious bursal disease virus, (c) the GO, and (d) the GO-Ag agent. Regenerated from [229].

As could be realized from the cases mentioned above, the surface physiochemical properties of GO, rGO and the structures based on these nanocarbons exhibit essential roles in their antiviral performance, influencing cells viability [234,235]. In this context, it was observed that the nano-topology of the graphene layers have a significant implication on the physical/mechanical properties of graphene augmented alumina nanofiber scaffolds, which in turn plays an important role in their antiviral performance against human pathogenic viruses (HPeV1 and IAV) through binding with viruses. Since the performances of graphene materials rely on surface-dependent reactions, their concentration and the exposure time period should also be important factors influencing their overall antiviral activity. A good example here is the work of Yang et al. [236] who investigated the concentration-dependent antiviral performance of the curcumin-loaded  $\beta$ -cyclodextrin functionalized sulfonated graphene composite (GSCC) toward respiratory syncytial virus (RSV). The latter is an enveloped virus with negative-sense single-stranded RNA, belonging to the *Paramyxoviridae* family. This virus causes respiratory disease in infants and young children [237]. The incubation of RSV with different concentrations of GSCC (0–5  $\mu$ g/mL) prior to the infection demonstrated the dose-dependent performance of the graphene material for the inactivation of the virus. A GSCC concentration of 1.25  $\mu$ g/mL could significantly reduce the viral titers, while the viral titers could not be detected at all at the concentration of 2.50  $\mu$ g/mL, indicating that the virus had lost the ability to infect cells. It was further shown that GSCC could block the receptors of Human laryngeal epithelial type 2 (HEp-2) cells, providing an inhibitory role against the infection [236].

Here, it is relevant to mention about the antiviral performance of carbon quantum dots (CQDs), which are categorized as mainly  $sp^2$  graphitic structures with sizes of typically less than 10 nm [238,239].

Due to their structural features, CQDs are capable of being functionalized with various functional groups to provide antiviral activities. For instance, CQDs functionalized with boric acid showed antiviral activity against HCoV-229E. Here, two mechanisms were found to be responsible for antiviral activities: 1) the prevention of the infectious interactions between host cells and viruses, achieved by the attachment of CQDs (with an average diameter of around 7 nm) to the S-protein of viruses; and 2) the ability of CQDs to inhibit the RNA genomic replication. The presence of boronic acid functions proved to be vital for revealing the antiviral activity [240]. Similar results were obtained by Barras et al. [241] who reported on the ability of 4-aminophenylboronic acid hydrochloride functionalized carbon nanodots to prevent HSV-1 infection. Fig. 4 highlights the antiviral activity of CQDs.

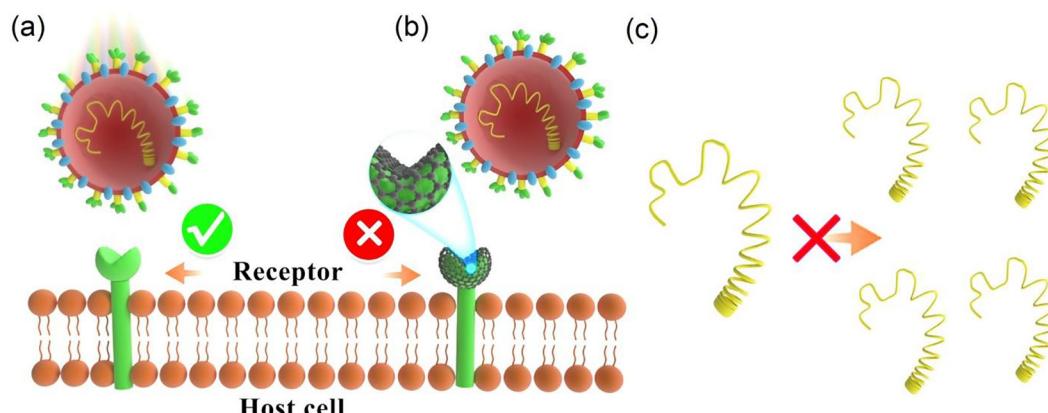
In examples highlighted above, the presence of surface functional groups on graphene materials exhibit an important role in binding of

the antiviral agent to the virus species. However, molecular dynamics simulations have confirmed the binding capability of graphene as well [242,243]. For example, simulations conducted by Raval et al. [242] show a strong binding efficiency between pristine multilayer graphene produced by mechanical exfoliation, and spike receptor binding domain of SARS-CoV-2 virus. In this case, the binding energy between graphene flakes and the virus increased with increasing the number of graphene layers of the flakes. Accordingly, a value of around  $-28.01$  Kcal/mol was calculated for the changes of Gibbs free energy involved in the binding process for graphene flakes containing seven layers. It was discussed that the number of edge  $sp^3$ -type carbon atoms increases with increasing the layers, promoting the surface reactivity of the graphene material.

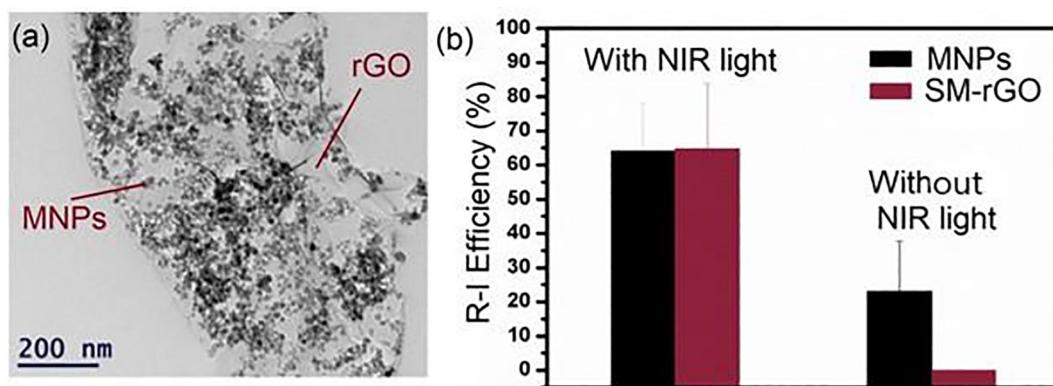
The other point that deserves attention is that graphene materials can be loaded with magnetic materials, and therefore, can provide with extra benefits associated with the magnetic properties obtained. For example, Deokar et al. [244] produced sulfonated magnetic nanoparticles (MNPs) loaded on rGO (SMRGO). Upon irradiation of the composite with near-infrared light, the nanocomposite material could effectively capture and photothermally destroy HSV-1 with an efficiency of around 99.99%, superior to that of magnetic nanoparticles alone, as can be realized from Fig. 5. The excellent performance of the graphene-based material was attributed to its virus capture efficiency, high surface area, and excellent photothermal properties of graphene, combined with the electrostatic interactions between MNPs with viral particles [244].

In addition to the examples provided on the antiviral properties of graphene-based materials mentioned above, the use of graphene in the process of synthesizing 2D antiviral drugs has also been reported. For instance, Mohammadifar et al. [245] produced 2D hyperbranched polyglycerol via a bottom-up graphene-assisted approach. It was demonstrated that the sulfated 2D hyperbranched polyglycerol structure fabricated using this strategy provides a higher degree of interactions with viral proteins of enveloped viruses (HSV-1, EAV and COVID-19) in comparison with the 3D version. The higher activity of the 2D structure was attributed to its greater surfaces at the same mass. As the result, more sulfate groups would be accessible on the 2D drug, which leads to the stronger interaction of the drug with the heparan sulfate receptors on the virus surfaces.

The state-of-the-art knowledge about the antiviral performances of graphene based materials, summarized above indicates several mechanisms by which graphene materials can potentially combat coronaviruses, perhaps, including COVID-19. Despite the valuable knowledge available, there are still various ambiguities and controversies involved in the antiviral application of graphene materials, including the virus mutation, the interactions between graphene and various



**Fig. 4.** The schematic representation concerning the antiviral activity of functionalized graphene QDs. (a) The binding interaction between the S protein of the virus (HCoV-229E) and host cell receptor causes viral diseases. (b) Such binding can be inhibited by the presence of ODS. (c) This mechanism can lead to the inhibition of the viral genome replication. Generated based on information extracted from [240].



**Fig. 5.** (a) TEM image of SMRGO highlighting the presence of iron nanoparticles (5–25 nm) on rGO sheets. (b) The relative percentage of the cell infection (R-I) before and after NIR irradiation. Regenerated from [244]. Copyright 2017, with permission from ACS Publications.

human genetics, side effects, and the associated cytotoxicity [246–251]. These issues should be considered in future studies.

## 7. Remarks and conclusions

The virus outbreaks that threaten the health of people worldwide provide the motivation to search for efficient antiviral agents. Given this, the current article concerned the antiviral performances of selected nanomaterials, with an emphasised on the antiviral performances of graphene-based materials. In terms of drug development, there are two strategies for combating coronaviruses including COVID-19, comprising drug repurposing and the discovery of novel drugs. Following the second strategy, Table 1, provides a summary of the performances of some antiviral agents, to inactivate coronaviruses, comprising iron oxide and silver nanoparticles, as well as

nanostructured aluminum 6063, and copper alloys. While appropriate antiviral performances can be achieved using these materials, other parameters such as the safety, toxicity, and cost of antiviral agents can play an important role in the possibility of their large scale application. Among the novel antiviral materials highlighted in Table 1, graphene-based materials may provide advantages of large availability, non-toxicity and low-cost.

Fig. 6 summarizes the main antiviral performances of graphene-based materials discussed in this article. Graphene materials show excellent inhibitory antiviral effects against enveloped and non-enveloped viruses, including RNA and DNA viruses. These performances which are attributed to the physicochemical properties exhibited on the surfaces of these materials, can be used to control the COVID-19 pandemic. Therefore, knowing the possible interactions between coronaviruses and graphene-based materials has been the

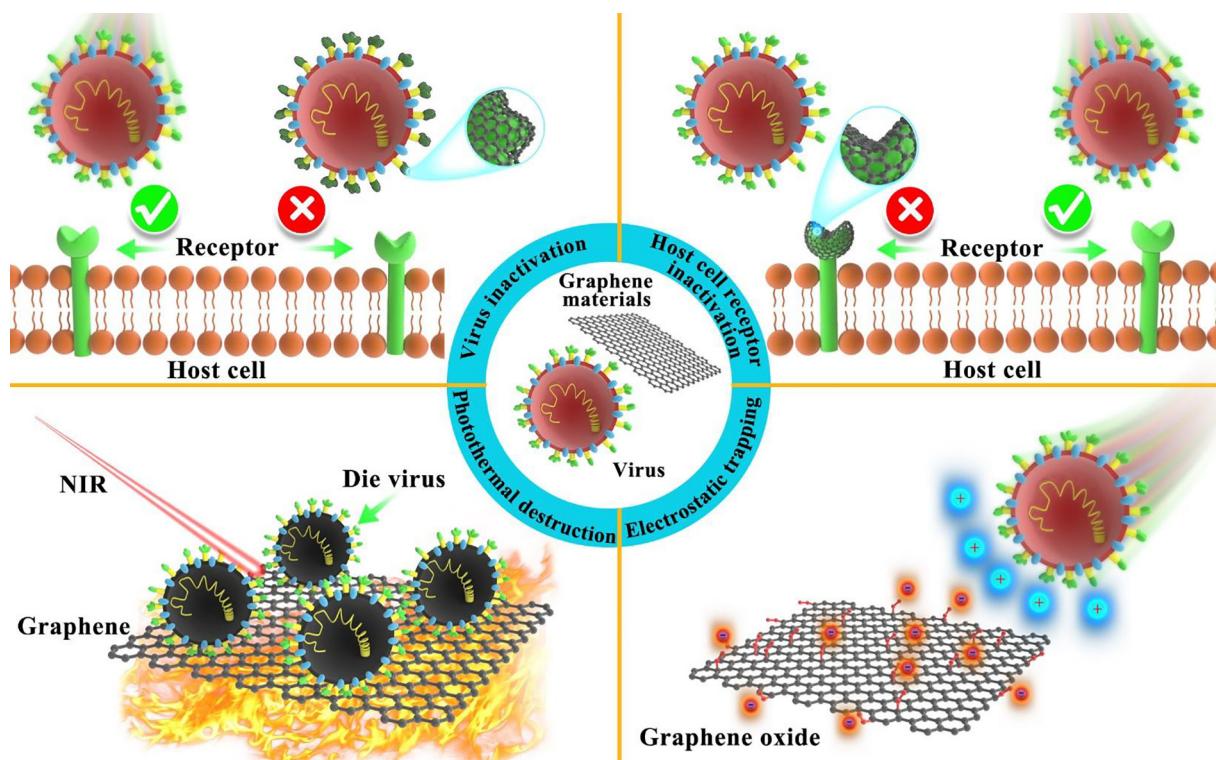
**Table 1**

Summary of the antiviral activities of selected nanomaterials against a variety of enveloped (+) and non-enveloped (-) viruses, comprising feline coronavirus (FCoV), infectious bursal disease virus (IBDV), pseudorabies virus (PRV), porcine epidemic diarrhea virus (PEDV), human immunodeficiency virus (HIV), rhinovirus (RV-16), herpes simplex virus type 1 (HSV-1), transmissible gastroenteritis virus (TGEV), MERS, HIV-1, Respiratory syncytial virus (RSV), influenza A virus, rhinovirus 2, adenovirus type 1 and vaccinia virus.

| Material (concentration)  | Type of virus  | Genome  | Antiviral activity   |
|---|--|---|--|
| GO; GO-Ag (0.1 mg/ml against FCoV, and 1 mg/ml against IBDV)  | FCoV (+); IBDV (-)   | FCoV (RNA); IBDV (RNA)  | 16.3% (GO <sub>x</sub> against FCoV); -0.4% (GO against IBDV); 24.8% (GO-Ag against FCoV); 22.7% (GO-Ag against IBDV)* [229]   |
| GO (6 µg/mL)  | PRV (+); PEDV (+)  | PRV (DNA); PEDV (RNA)   | Reduction from $5 \times 10^7$ to $2.5 \times 10^5$ pfu/mL [232]   |
| Cationic CQDs (125 µg/mL)   | PEDV (+)   | RNA   | Inhibition the virus entry over 50% [258]  |
| Graphene quantum dots   | HIV (+)  | RNA   | $IC_{50}$ ( $37.6 \pm 6.23$ µg/mL); $EC_{50}$ ( $>19.90$ µg/mL)** [259]  |
| Al 6063 surfaces  | RV-16 (-)  | RNA   | 3–4 $\log_{10}$ reduction viable virus [260]   |
| Sulfonated magnetic nanoparticles functionalized with rGO (SMRGO) (100 ppm); Spherical magnetic Fe nanoparticles (MNPs) (100 ppm) | HSV-1 (+)  | DNA   | without NIR light: 34.38% (MNPs) and 34.97% (SMRGO); Under NIR light: 79.06% (MNPs) and 99.99% (SMRGO) [244]   |
| Spherical Ag nanoparticles (NPs < 20 nm); Ag nanowires (D = 60 nm, Ag NW60), and (D = 400 nm, Ag NW400) / 3.125–12.5 µg/mL        | TGEV (+)   | RNA   | The percentage reduction at different concentrations. At 3.125 µg/mL: 7.05% (Ag NPs), 18.04% (Ag NW60) and 15.48% (Ag NW400); At 6.25 µg/mL: 32.12% (Ag NPs), 38.06% (Ag NW60) and 28.94% (Ag NW400); At 12.5 µg/mL: 67.35% (Ag NPs), 53.90% (Ag NW60) and 58.65% (Ag NW400) [261] |
| Gold nanorod-based heptad repeat 1 peptide inhibitor  | MERS (+)   | RNA   | More than 90% [262]  |
| Copper oxide-containing filter/ 5% (wt/wt) copper oxide particles   | HIV-1 (+); RSV (+); Influenza A (+); Rhinovirus 2 (-); Adenovirus type 1 (-); Vaccinia virus (+) | HIV-1 (RNA); RSV (RNA); Influenza A(RNA); Rhinovirus 2 (RNA); Adenovirus type 1 (DNA); Vaccinia virus (DNA) | $\log_{10}$ reduction: 4.6 (HIV-1); 1.5 (RSV); 1.77 (Influenza A); 2 (Rhinovirus 2); 2.2 (Adenovirus type 1); 0.47 (Vaccinia virus) [263]  |
| Copper-graphene nanocomposite (5 µM)  | Influenza A  | RNA   | ~50% reduction [264]   |

\* Antiviral activity % =  $(\log_{10} (\text{TCID}_{50}/\text{mL of virus}) - \log_{10} (\text{TCID}_{50}/\text{mL of treatment})) / \log_{10} (\text{TCID}_{50}/\text{mL of virus}) \times 100\%$

\*\*  $IC_{50}$  is the half maximal inhibitory concentration in vitro for inhibition the activity of RNA-dependent DNA polymerase.  $EC_{50}$  is the half maximal effective concentration for reduction 50% the HIV-1-induced cytopathic effect in MT-4 cells.



**Fig. 6.** Summary of main mechanisms involved in the antiviral performances of graphene materials, comprising the inhibition of the virus/cell binding, electrostatic trapping and the photothermal destruction.

center of the research activities in the field. Graphene and its derivatives exhibit the ability to inactivate different viruses through various mechanisms, namely photothermal activity and inhibit cellular infection by binding the nanomaterials to the S-protein of viruses or host cell receptors. Two important characteristics of graphene materials are based on their capability to be functionalised, and also be used as the substrate to homogeneously load other antiviral agents. Given this, those characteristics of graphene materials influencing their antiviral performances include the surface area, charge density and the concentration of graphene materials, as well as the type and size of loaded particles, the type and degree of functional groups. On the other hand, the virus characteristics such as being enveloped or non-enveloped viruses, and the time of usage the nanomaterials (virus pre-treatment, virus co-treatment, cell pre- and post-treatment) also play essential roles in determining the antiviral activity of graphene-based materials. Finally, it should be emphasised that carbon materials can provide multi-functional performances which can be employed for the decomposition of organic pollutants [252,253], adsorption of heavy metals [254] and killing of infectious pathogens, increasing the efficiency of carbons towards environmental protections. The development of efficient carbon-based materials can support the global efforts towards combat bacterial [255] and viral infections.

#### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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